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Studies on a New 1,5-Benzothiazepine Derivative (CRD-401). IV. Coronary Vasodilating Effect and Structure-Activity Relationship[1]

Taku Nagao, Masanori Sato, Hiromichi Nakajima, and Akio Kiyomoto

The Biological Research Laboratory, Tanabe Seiyaku, Co., Ltd.[2]

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The coronary vasodilating action of 1,5-benzothiazepine derivatives and the structure-activity relationship were examined in the anesthetized dog. 2-(4-Methoxyphenyl), 3-acyloxy or alkyloxy, 5-dimethylaminoethyl and 7-hydrogen moieties were important for vasodilation. The action of the derivatives was found to be stereospecific for the *d-cis*-isomer. Based on these findings, it can be concluded that *d*-3-acetoxy-*cis*-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride (CRD-401) was the most potent compound among the derivatives tested. The metabolites of *dl*-isomer of CRD-401, *i.e.* deacetyl and deacetyl-O- or N-demethyl compounds, were less active and less toxic than the parent compound.

In the previous papers,[3] it was reported that a new 1,5-benzothiazepine derivative, 3-acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4-(5H)-one hydrochloride had a potent coronary vasodilating activity without increasing myocardial oxygen consumption. Among its four stereoisomers, the *d-cis*-isomer (CRD-401) showed the strongest activity.

In the present study, a structure-activity correlation in a series of compounds related to the new 1,5-benzothiazepine derivative was determined with respect to the coronary vasodilating activity in the anesthetized dog.

Method

Coronary Sinus Outflow——Male mongrel dogs weighing 14.5 to 22 kg were anesthetized with 30 mg/kg of intravenously administered sodium pentobarbital. The trachea was intubated, and ventilation was maintained by a positive pressure respirator (Takashima, Model 101). The chest was opened by removal of a portion of the right fourth rib, and the heart was exposed. After heparinization (5 mg/kg, *i.v.*), a Morawitz cannula[4] was inserted into the coronary sinus through the right auricle and the sinus blood was led into the right external jugular vein *via* a rubber tube. Coronary sinus outflow was measured by an electromagnetic flowmeter (Nihon Kohden, MF-2) which was placed in the circuit. Femoral arterial pressure was obtained *via* a pressure transducer and heart rate was measured by a cardiotachography, triggered by the arterial pulse. All measurements were recorded simultaneously on a multipurpose polygraph (Nihon Kohden, RM-150).

Each drug solution was injected into the left femoral vein through an inserted catheter.

Results shown in Table I to Table IV were obtained after intravenous administration of 0.2 mg/kg of 1,5-benzothiazepine derivatives and papaverine. The coronary vasodilating activity of the test compound was expressed as the potency relative to papaverine (papaverine=1). Each value is the mean of three to seven experiments.

Coronary Arterial Flow——Male dogs were anesthetized and heparinized and the heart was exposed in a similar manner to that mentioned above. According to the method described by Eckenhoff,[5] the left anterior descending coronary artery was perfused with the blood of the left common carotid artery through

1) Part III: T. Nagao, M. Sato, Y. Iwasawa, T. Takada, R. Ishida, H. Nakajima, and A. Kiyomoto, *Japan. J. Pharmacol.*, 22, 467 (1972).
2) Location: *2-2-50, Kawagishi, Toda-Shi, Saitama.*
3) *a*) M. Sato, T. Nagao, I. Yamaguchi, H. Nakajima, and A. Kiyomoto, *Arzneim.-Forsch.*, 21, 1338 (1971); *b*) T. Nagao, M. Sato, H. Nakajima, and A. Kiyomoto, *Japan. J. Pharmacol.*, 22, 1 (1972).
4) P. Morawitz and A. Zahn, *Zentralb. f. Physiol.*, 26, 465 (1912).
5) J.E. Eckenhoff, J.H. Hafkenschiel, and C.M. Landmesser, *Amer. J. Physiol.*, 148, 582 (1947).

an extracorporeal loop. An electromagnetic flowmeter was introduced into the loop to measure the coronary artery flow. Femoral arterial pressure was obtained *via* a pressure transducer and recorded simultaneously with the coronary flow on a multipurpose polygraph.

Each drug solution having no influence on the systemic blood pressure was injected into the loop close to the perfusing artery in volume of less than 0.25 ml for 10 seconds. Fig. 1 showed the case in which the drug solution was administered by this procedure.

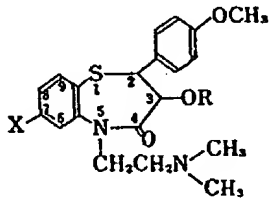
The 1,5-benzothiazepine derivatives were synthesized by Kugita, *et al.*[6]

Result

1. Comparison of Coronary Vasodilating Activity between 2,3-*cis*- and *trans*-Isomers

The potencies of *cis*- and *trans*-isomers of four pairs of benzothiazepine derivatives were compared and the results were summarized in Table I. The *cis*-isomers all produced strong increasing effect on the coronary sinus outflow, whereas the activities of *trans*-isomers were very weak or hardly detectable. Therefore, the *cis*-isomers of the test compounds were used throughout the following experiments.

Table I. Comparison of Coronary Vasodilating Activity between 2,3-*cis*- and *trans*-Isomers



No	X	R	Salt		Potency[a]
I	H	H	HCl	*cis*	1.9
II	H	H	HCl	*trans*	<0.1
III	H	$COCH_3$	HCl	*cis*	3.5
IV	H	$COCH_3$	HCl	*trans*	<0.1
V	Cl	H	HCl	*cis*	0.8
VI	Cl	H	HCl	*trans*	<0.1
VII	Cl	$COCH_3$	HCl	*cis*	3.3
VIII	Cl	$COCH_3$	HBr	*trans*	0.1

a) Potencies were expressed as papaverine=1. The compounds were administered intravenously (0.3 mg/kg).

2. Effect of Aryl Substitution in the 2 Position

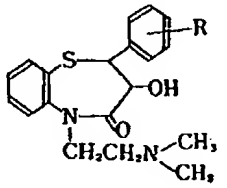
Among the 2-aryl derivatives tested, 4-methylphenyl (X) and 4-methoxyphenyl (I) analogues exerted high activities (Table II). Increase in the number of methoxy group caused activity loss to a great extent (XI, XII). Mono- and di-chlorophenyl analogues (XIV, XV) and 4-hydroxyphenyl analogue (XIII) were far less active or practically inactive. As examined by intraarterial administration, duration of the action of 4-chlorophenyl analogue (XIV) was found to be shorter than that of 4-methoxyphenyl analogue (I) (Fig. 1A).

3. Effect of Alkyl Substitution in the 5 Position

As shown in Table III, only tertiary amino compounds were active and the secondary or quaternary amino compounds were inactive. Reduction of the activity resulted from the increase in the distance between nitrogen atom in the skeleton and that in the side chain of the tertiary amino compounds (I, XVIII, XX, XIX). In addition, it was found that the

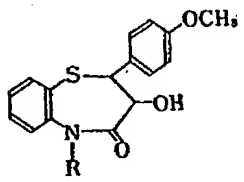
6) H. Kugita, H. Inoue, M. Ikezaki, M. Konda, and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), 19, 595 (1971).

Table II. Effect of Aryl Substitution in the 2 Position



No	R	Salt	Potency
IX	H	HCl	0.2
X	4-Me	HCl	1.8
I	4-MeO	HCl	1.9
XI	3,4-diMeO	HCl	0.2
XII	3,4,5-triMeO	HBr	0.1
XIII	4-OH	HCl	0.1
XIV	4-Cl	HCl	<0.1
XV	2,4-diCl	HCl	0.1

Table III. Effect of Alkyl Substitution in the 5 Position



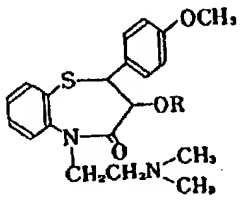
No	R	Salt	Potency
XVI	H		<0.1
XVII	$CH_2CH_2N(CH_3)H$	HCl	0.1
I	$CH_2CH_2N(CH_3)_2$	HCl	1.9
XVIII	$CH_2CH_2N(C_2H_5)_2$	HCl	0.8
XIX	$(CH_2)_2N(CH_3)_2$	HCl	0.4
XX	$CH(CH_3)CH_2N(CH_3)_2$	$(COOH)_2$	1.4
XXI	$CH_2CH_2\overset{+}{N}(CH_3)_3$	I^-	0.1
XXII	$(CH_2)_2\overset{+}{N}(CH_3)_2C_2H_5$	Br^-	<0.1
XXIII	$(CH_2)_2\overset{+}{N}(CH_3)_3$	I^-	0.1

dimethylamino analogues (I, XX) were more active than the diethylamino analogue (XVIII). Non-substituted compound (XVI) was inactive. These results shown in Table III indicate that the dimethylaminoethyl analogue (I) was the most active compound among the 5-alkyl derivatives tested.

4. Effect of Acyloxy and Alkyloxy Substitution in the 3 Position

In general, 3-acyloxy and 3-alkyloxy derivatives showed high activities (Table IV). Among them, acetoxy (III) and ethoxycarbonyloxy (XXIX) analogues were the most active

Table IV. Effect of Acyloxy or Alkyloxy Substitution in the 3 Position



No	R	Salt	Potency
I	H	HCl	1.9
III	$COCH_3$	HCl	3.5
XXIV	COC_2H_5		0.5
XXV	COC_3H_7		1.2
XXVI	COC_4H_9 (n)		2.5
XXVII	COC_4H_9 (i)		2.1
XXVIII	COC_5H_{11} (n)		1.8
XXIX	$COOC_2H_5$		3.5
XXX	COC_6H_5	HCl	0.7
XXXI	CH_3	HBr	3.0
XXXII	C_2H_5	$HClO_4$	2.5
XXXIII	C_3H_7	$HClO_4$	2.0
XXXIV	$CH_2C_6H_5$	HCl	1.3

and methoxy (XXXI), ethoxy (XXXII) and valeryloxy (XXVI) analogues were also highly active. On the other hand, compound with propionyloxy (XXIV) or butyryloxy (XXV) moiety was found to be less active. As shown in Fig. 1A, acetyloxy analogue (III) was longer acting than the hydroxy analogue (I).

5. Effect of Chlorine Substitution in the 7 Position

As illustrated in Table I and Fig. 1A, substitution of hydrogen (I, III) with chlorine (V, VII) in the 7 position of 3-hydroxy-2-(4-methoxyphenyl) or 3-acetoxy-2-(4-methoxyphenyl) derivatives led to a slight reduction of activity. On the other hand, the activity of 3-hydroxy-2-(4-chlorophenyl) derivatives was not affected by replacement of hydrogen (XIV) with chlorine (XXXV) in the 7 position.

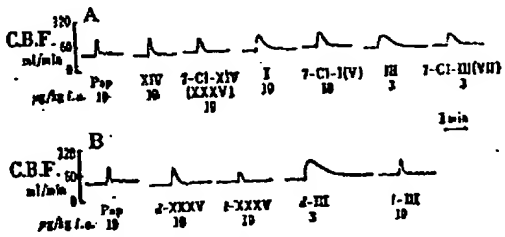


Fig. 1. Effects of Cl-Substitution in the 7 Position (A) and of the Optical Isomers (B) of the *cis*-2,3-Dihydro-1,5-benzothiazepine Derivatives on Coronary Blood Flow

The compounds were administered intraarterially in the anesthetized dog. Pap = papaverine, C. B. F. = coronary blood flow

6. Optical Isomers

As to the optical isomers of the two benzothiazepine derivatives (III, XXXV), the coronary vasodilating activity was examined by intraarterial administration. As shown in Fig. 1B, the *d*-isomers of both III and XXXV exhibited stronger and longer-lasting activity than the corresponding *l*-isomers. This was especially remarkable in the case of III.

Discussion

In the present study, the coronary vasodilating actions of a series of 1,5-benzothiazepine derivatives were examined by intravenous or intraarterial administration in the anesthetized

dog. In general, the actions of these derivatives were found to be longer than that of papaverine.

Based on our present experimental results, it can be said that the following elements are important for manifestation of the strong and long-lasting coronary vasodilating activity: 1) 4-methoxyphenyl at position 2, 2) acetoxy or ethoxycarbonyloxy at position 3, 3) dimethylaminoethyl at position 5, 4) hydrogen at position 7 and 5) *d-cis* form. Thus it can be concluded that *d*-3-acetoxy-*cis*-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride (the *d-cis*-isomer of III, CRD-401) was the most potent compound so far tested. Although the *dl-cis*-3-ethoxycarbonyloxy analogue (XXIX) showed the same potency as the *dl-cis*-3-acetoxy analogue (III), the acute toxicity of the former was stronger than that of the latter.

Vasodilating action of propionyl and butyryl analogues was weaker than that of acetyl or valeryl analogue. Therefore, no direct relationship was observed between the length of carbon chain of fatty acid and the coronary vasodilating activity in ester derivatives. On the contrary, the longer in the carbon chain, the weaker in potency was found in ether derivatives.

In 5-alkyl derivatives (Table III), compound with dimethylaminoethyl, diethylaminoethyl or dimethylaminopropyl moiety was active in coronary vasodilation. In the derivatives of thiazesim, *i.e.*, in 3-unsubstituted 2,3-dihydro-1,5-benzothiazepin-4(5H)-one derivatives, these moieties were also reported to be effective in calming rats with lesions in the septal area of the brain.[7]

In this and previous papers,[8] it was shown that the coronary vasodilating and some other pharmacological activities of the *d-cis*-isomer of III was more potent than that of the *l-cis*-isomer. The *d-cis*-isomer of XXXV was also found to produce stronger vasodilating action than the *l-cis*-isomer. On the other hand, the optical isomers of thiazesim had essentially the same activity as the racemate in depressing the central nervous system and in the toxicity.[8]

It has been demonstrated[3b] that the vasodilating effect of the *d-cis*-isomer of III (CRD-401) was not affected by pretreatment with such blocker as atropine, propranolol or diphenhydramine. The compound also did not increase the myocardial oxygen consumption in the anesthetized dog.[3a] From these evidences, it was infered that CRD-401 exerts its vasodilating effect by acting directly on blood vessel.[3b]

On the other hand, diazepam, the chemical structure of which is somewhat similar to CRD-401, is said to act as a specific ganglion stimulant, since its coronary vasodilating action is inhibited by small doses of atropine or ganglion-blocking agents.[9] Therefore, the mechanism of CRD-401 in producing cornary vasodilating effect seems to be different from that of diazapam.

Meshi, *et al.*[10] reported that metabolites of CRD-401 in rats were the deacetyl-, deacetyl-O-demethyl- and deacetyl-N-demethyl-CRD-401, each of which was the *d-cis*-isomer of I, XIII and XVII, respectively. Compound I elicited a potent coronary vasodilating activity in a dose of 0.2 mg/kg *i.v.* and produced a slight decrease in systemic blood pressure, while the heart rate was unchanged in the anesthetized dog. On the other hand, XIII and XVII produced no effect on coronary blood flow, systemic blood pressure and heart rate at the same dose as above. Besides these cardiovascular activities, toxicities of the metabolites were also examined. It was found that the acute toxicities (LD50, mg/kg *i.v.*) of III, I, XIII, and XVII in mice were 64, 83, 122, and 94, respectively. Therefore, the metabolites of III

7) J. Krapcho and C.F. Turk, *J. Med. Chem.*, 9, 191 (1966).
8) J. Krapcho, C.F. Turk, and J.J. Piala, *J. Med. Chem.*, 11, 361 (1968).
9) R.M. Abel, R.L. Reis, and R.N. Staroscik, *Br. J. Pharmac.*, 39, 261 (1970); *idem*, *ibid.*, 38, 620 (1970).
10) T. Meshi, J. Sugihara, and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), 19, 1546 (1971).

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were less toxic than their parent compound (III). These results also indicate that the deacetyl compound of III is still active, whereas the demethyl compounds of III are less active.

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